Behavioral/Systems/Cognitive

Visual Fixation as Equilibrium: Evidence from Superior Colliculus Inactivation

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During visual fixation, the image of an object is maintained within the fovea. Previous studies have shown that such maintenance involves the deep superior colliculus (dSC). However, the mechanisms by which the dSC supports visual fixation remain controversial. According to one view, activity in the rostral dSC maintains gaze direction by preventing neurons in the caudal dSC from issuing saccade commands. An alternative hypothesis proposes that gaze direction is achieved through equilibrium of target position signals originating from the two dSCs. Here, we show in monkeys that artificially reducing activity in the rostral half of one dSC results in a biased estimate of target position during fixation, consistent with the second hypothesis, rather than an inability to maintain gaze fixation as predicted by the first hypothesis. After injection of muscimol at rostral sites in the dSC, fixation became more stable since microsaccade rate was reduced rather than increased. Moreover, the scatter of eye positions was offset relative to preinactivation baselines. The magnitude and the direction of the offsets depended on both the target size and the injected site in the collicular map. Other oculomotor parameters, such as the accuracy of saccades to peripheral targets and the amplitude and velocity of fixational saccades, were largely unaffected. These results suggest that the rostral half of the dSC supports visual fixation through a distributed representation of behaviorally relevant target position signals. The inactivation-induced fixation offset establishes the foveal visual stimulation that is required to restore the balance of activity between the two dSCs.

Introduction

In primates, the appearance of an object in the visual field can trigger a saccadic eye movement that quickly orients the fovea toward its location. One fundamental question about this goal-directed oculomotor response concerns the brain mechanisms by which sets of motor commands are associated with signals evoked by a sensory event. In the massive network of neurons distributed in the brain, the deep superior colliculus (dSC) constitutes a major interface between sensory signals and motor commands for orienting the fovea (Sparks, 1986; Hall and Moschovakis, 2004; Gandhi and Katnani, 2011).

Over the last two decades, the dSC was commonly considered as composed of two zones: a fixation zone located in its rostral portion and a saccade zone located more caudally (Munoz and Guitton, 1991; Munoz and Wurtz, 1993a,b). According to this view, the fixation zone would contain neurons involved in maintaining gaze directed toward a foveal target, whereas neurons in the saccade zone would issue commands for generating gaze shifts toward peripheral targets. The fixation and saccade zones were considered as antagonist systems that inhibit each other in a push–pull manner.

Subsequent findings, however, have cast doubt on this dichotomist view. First, observations have accumulated to support the idea that the locus of dSC activity, whether rostral or caudal, participates in the selection of a target to foveate (Carello and Krauzlis, 2004; McPeek and Keller, 2004), pursue (Krauzlis et al., 2000; Hafed and Krauzlis, 2008; Nummela and Krauzlis, 2010) or attend to (Cavanaugh and Wurtz, 2004; Müller et al., 2005; Lovejoy and Krauzlis, 2010). Second, perturbation experiments have shown that electrical microstimulation of the rostral dSC alters the trajectory of saccades like caudal microstimulations do (Gandhi and Keller, 1999). Third, the rostral dSC contains neurons with movement field properties similar to those recorded more caudally; these neurons increase their firing rate during microsaccades and exhibit selectivity for a limited range of movement directions and amplitudes (Hafed et al., 2009; Hafed and Krauzlis, 2012). Altogether, these observations support a different view of the collicular control of the gaze orienting response. Rather than being composed of two separate zones, the dSC would form a continuous map where the population of active neurons encodes the target location in oculocentric coordinates (Sparks et al., 1976; Krauzlis et al., 1997, 2004). Fixation would then correspond to an equilibrium state in which activity distributed across the left and right dSCs determines gaze direction, and microsaccades would result from transient imbalances between fluctuat-

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ing target position signals issued by the two dSCs (Hafed et al., 2008, 2009). According to this alternative hypothesis, inactivation of rostral sites in the dSC should modify this equilibrium and alter the encoding of a foveal target.

In this paper, we present evidence for an oculomotor disorder that suggests such an altered encoding. This deficit mirrors a similar one observed during smooth pursuit (Hafed et al., 2008) and demonstrates that the control of foveation by the dSC arises through a population coding similar to that shown for the generation of saccades (Lee et al., 1988).

Materials and Methods

Subjects and surgical procedures. Two adult male monkeys (A and W; *Macaca mulatta*; 12–15 kg) were used for this study. They were prepared using standard surgical techniques described in detail previously (Krauzlis, 2003). Briefly, under isoflurane anesthesia and aseptic conditions, a search coil was placed on the sclera under the conjunctiva of one eye to measure eye movements with the electromagnetic induction technique (Fuchs and Robinson, 1966; Judge et al., 1980), a head holder was attached to the skull to restrain the head in the standard stereotaxic position during experiments, and a recording chamber was affixed to the skull for single-neuron recording, electrical microstimulation, and reversible inactivation in the dSC (Hafed et al., 2008). All experimental protocols were approved by the Salk Institute's Animal Care and Use Committee and complied with U.S. Public Health Service policy on the humane care and use of laboratory animals.

Eye movement recording. Experiments were controlled by a computer using the Tempo software package (Reflective Computing), and a second computer running the Psychophysics Toolbox in Matlab (MathWorks) (Brainard, 1997; Pelli, 1997) acted as a server device for presenting the visual stimuli. Stimuli were presented with a video monitor (75 Hz, ~20 pixels per degree) at a viewing distance of 41 cm. Eye movements were recorded using standard phase detector circuits (Riverbend Instruments). All data and events related to the onset of stimuli were stored on disk during the experiment (1 kHz sampling rate).

Behavioral tasks. The primary behavioral task used in this study required the monkeys to initially fixate a central target and then make a saccade to a peripheral one. At the beginning of each trial, the monkeys were given a grace period of 400 ms to acquire initial fixation of the central target, which was presented over a uniform gray background (18 cd/m^2). In different blocks of trials, this target could either be a small white spot (~0.03° radius), a medium blurred spot (white circle of 1° radius with Gaussian-blurred edges), or a large blurred spot (white circle of 2° radius with Gaussian-blurred edges) of 65 cd/m^2 luminance. For the medium and large targets, circular stimuli with smooth, blurred edges were used to discourage the monkeys from fixating particular corners or edges. Different target sizes were used because we hypothesized that larger target sizes would recruit larger populations of neurons in the dSC during fixation, as was observed during neural recordings in the dSC (Hafed and Krauzlis, 2008). After the central target was foveated, the monkeys were required to maintain gaze within a spatial window around the target (typically 1–1.5° radius for the smallest target size and 3° for the larger ones) for a variable fixation interval (1500–2500 ms). The central target was then extinguished, and after a gap of 200 ms, a second small white target (~0.03° radius) appeared in the peripheral visual field for 100 or 1000 ms. The location of the peripheral target was pseudorandomly selected from four predefined locations ±12° along either the horizontal or vertical meridian (positive values corresponding to rightward and upward positions). The brief target presentation (100 ms) was used to prevent visual guidance of saccades in the case where muscimol injection had led to a severe slowing of saccades (Hikosaka and Wurtz, 1985; Sparks et al., 1990; Aizawa and Wurtz, 1998; Quaia et al., 1998). A fluid reward was delivered to the monkeys if they maintained gaze within a spatial window around the peripheral target (3° radius) for at least 200 ms. In each experiment, we collected approximately 30 trials for each combination of stimulus conditions. Standard visually guided saccade tasks were also used to identify dSC inactivation sites, as explained below.

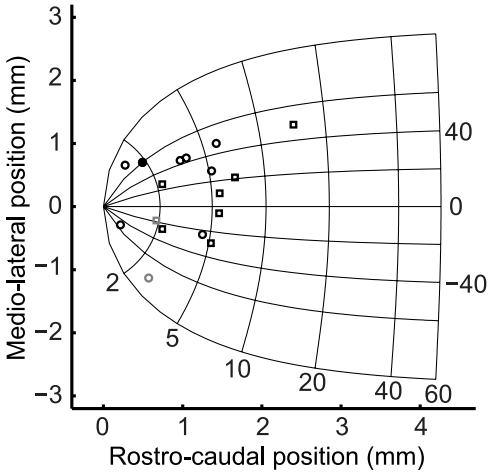

Figure 1. Distribution of muscimol injection sites within the dSC. Circle and square symbols correspond to the injections made in monkey A and W, respectively. The center of each site was estimated by the target location in retinotopic space that was associated with the largest saccade latency during a visually guided saccade task. This estimate does not reflect the entire extent of the inactivation. A spread of muscimol toward the rostral end of dSC must be considered even during those injections that were made at sites encoding target locations at 6° in the periphery (~1.5 mm caudal to the rostral border of the dSC). The filled black circle indicates the site for the postinjection data shown in Figures 2, 3, 6, and 8. For each site, a volume of 0.5 μl of muscimol was injected. The open gray symbols indicate the injections that led to nystagmus.

Reversible inactivation. Portions of the dSC of both monkeys were inactivated by local muscimol injections (0.5 μl, 5 μg/μl) using a custom-made apparatus modified from Chen et al. (2001). The injections were aimed at the intermediate and deep layers of the superior colliculus (1.8–2.5 mm below surface) and spanned a range of sites across the dSC map in 16 experiments. Two injections in the rostral end of the dSC (one in each monkey) were excluded from analysis because they caused severe horizontal nystagmus-like eye movements (Schiff et al., 1990; Munoz and Wurtz, 1993b), presumably due to a spread of muscimol into the pretectum, which is rostral to the dSC. We also injected sterile saline solution in two control sessions (one per monkey) at sites inactivated previously with muscimol. Injection of the entire volume of muscimol or saline was done over a period of ~30–40 min.

The inactivated sites were identified as follows. The day before each inactivation session, a site and depth were identified within the dSC using single-unit recording to measure movement fields of neurons at the recorded site, and electrical microstimulation (400 ms, 500 Hz, ~30 μA, biphasic pulses) to determine the direction and amplitude of evoked saccades. During the inactivation session, we confirmed our site by observing multiunit or single-unit saccade-related activity and/or by evoking saccades with microstimulation. The ability to successfully evoke saccades with microstimulation currents <30 μA was the criterion for proceeding with the inactivation experiment. Finally, the efficacy of each muscimol injection was verified by observing latency increases during a visually guided saccade task (Hikosaka and Wurtz, 1985; Sparks et al., 1990; Quaia et al., 1998). These latency increases were localized in the region of retinotopic space affected by our injection, and the location with the largest saccade latency was used as a quantitative estimate of the center of the inactivated site. A summary of these estimated centers of injection is shown in Figure 1. Approximately one-third of our injections were centered at sites in the far rostral pole of the dSC (the central 2–3° of the dSC map), with the remainder centered at slightly more caudal sites; all but one site was centered in the rostral half of the dSC. Because of drug spread, these estimates of the injection center do not reflect the entire extent of the inactivation. We previously measured the spread for our injections (muscimol, 0.5 μl, 5 μg/μl) by determining the range of saccades whose latency was increased during inactivation (Hafed et al., 2008, their Figs. 3, 8, 9); these inactivation maps show that even sites centered at ~5° affected neurons within the central 2–3° of the dSC map. These measurements of drug spread are consistent with previous work on mus-

cimol diffusion in the rat brain, which revealed a diffusion radius of 1.7 mm for an injected volume of 1 μl (Martin, 1991). Given the lower injection volumes used in the present experiments, we estimate a diffusion radius of ~1.5 mm.

Data analysis. The results presented in this paper are based on the data obtained before and after unilateral injections of muscimol (14 experiments) or saline solution (2 experiments) in the dSC of two monkeys. The data were analyzed using a software program that detected the onset and offset of the horizontal and vertical saccade components on the basis of velocity and acceleration thresholds (Krauzlis and Miles, 1996). The results of the automatic detection were checked by inspecting each trial individually and, if necessary, adjusted manually. Several behavioral parameters such as the latency, amplitude, duration, and peak velocity of each component (horizontal and vertical) of saccades were extracted automatically from detected movements. For each experiment, the values of each parameter measured during the control session were compared with the performance after muscimol injection using the nonparametric Mann–Whitney test. Paired comparisons (nonparametric Wilcoxon test) were also performed between the median values of the preinjection and postinjection data to extract the effects that were consistently observed across all experiments. Finally, an ANOVA was performed on the data collected in each monkey to test the effects of the injected site and target size on the average horizontal and vertical eye positions during the fixation interval.

Results

We reversibly and unilaterally inactivated portions of the rostral half of the dSC to test whether fixation of a central stationary target depended on the bilateral balance of activity across the dSC. In what follows, we show that the inactivation caused systematic offsets in eye position during fixation, consistent with our hypothesis. We then show that this disorder of eye position could not be attributed to a deficit in the generation of fixational saccades, as might be expected if the inactivation disrupted saccade-related activity in adjacent portions of the dSC. We also show that the size of the central target influenced not only the range of fixational saccade sizes, but also the magnitude of the eye position offsets caused by inactivation. Finally, we show that saccades to peripheral targets remained fairly accurate despite the offsets in starting eye position, indicating that the encoding of target locations outside the injected site was relatively unaffected.

Rostral dSC inactivation altered eye position during fixation

Muscimol injection in the rostral half of the dSC caused a shift in the scatter of eye positions when the monkey fixated the central target. Figure 2 illustrates this effect after an injection in the right dSC in one monkey. The horizontal (top) and vertical (middle) eye positions recorded while the monkey looked at a large target are plotted during the last 1500 ms of the fixation interval for 15 randomly selected trials. If one disregards the fixational saccades, one can observe that the eye position was stable (no drift) both before (left, Pre) and after muscimol injection (right, Post). Moreover, after the injection, there was a tendency for the eye position values to be offset toward the injected side (i.e., toward the right; positive values of horizontal eye position) and downward (negative values) compared to the preinjection performance (Fig. 2, summary Cartesian plots, bottom). Thus, in this sample session, inactivation of a region of the dSC corresponding to parafoveal locations in the upper left visual field caused an offset in eye position to the lower right direction, without otherwise disrupting the ability of the monkey to maintain a stable eye position.

When we repeated the experiment for the different sizes of the central target, we found that the magnitude of the eye position offset caused by the dSC inactivation depended on the size of the target, whereas the direction of the offset was largely unaltered for a given site. Figure 3*A* shows this effect, for the same experiment as in Figure 2, but for each target size individually (left, small target; middle, medium; right, large). In this figure, we plotted the average eye position measured for each trial and over the entire fixation interval, before (open circles) and after (closed circles) injection of muscimol. For comparison, Figure 3*B* shows the effects of injecting saline solution at the same collicular site in a separate, control experiment. As can be seen, before the injection of muscimol, the scatter of eye positions increased with the size of the target and tended to be deviated upward with a magnitude that increased with the target size as well. After muscimol injection, the eye positions were also more scattered with larger targets, but they were mostly directed toward the lower right quadrant relative to baseline. The average direction of the eye position offsets relative to the baseline before muscimol injection (335, 322, and 313° for the small, medium and large targets, respectively) was opposite the direction of target locations (in polar coordinates) encoded at the injected site (120°). In comparison,

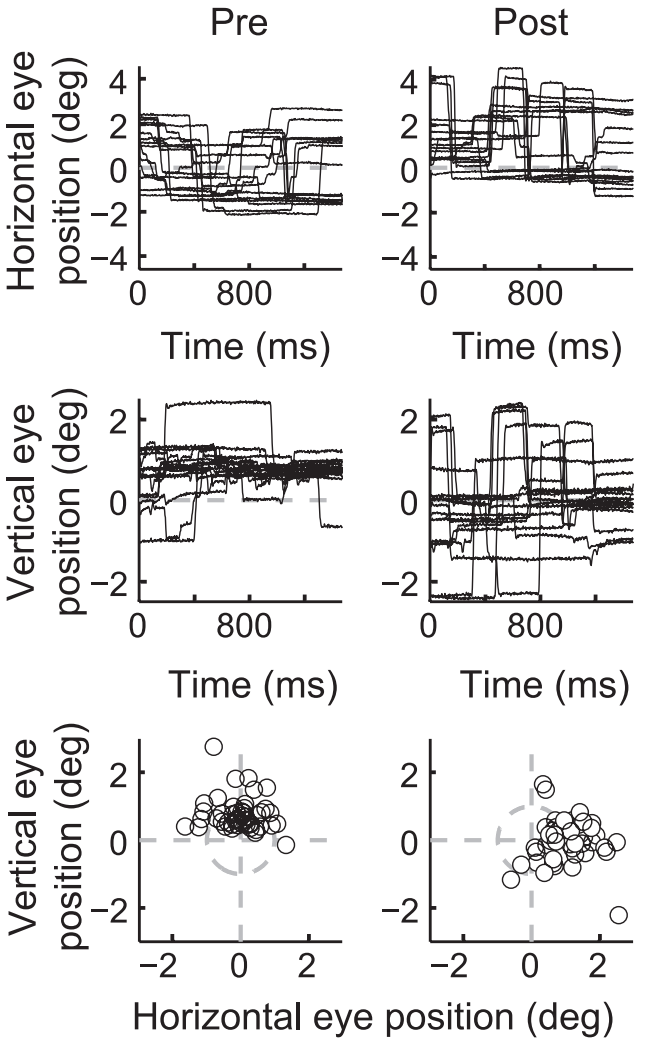

Figure 2. Sample experiment illustrating the fixation offset after muscimol injection in the right rostral dSC. The horizontal (top) and vertical (middle) eye positions recorded while the monkey looked at a large target are plotted during the last 1500 ms of the fixation interval for 15 randomly selected trials recorded before (Pre) and after muscimol injection (Post). Cartesian plots (bottom) illustrate the average eye position during fixation from all trials in the same session. These data show that the offset is rightward, i.e., toward the injected side.

local injection of saline solution at the same site did not produce any consistent offset in eye position. Thus, inactivation of the rostral dSC caused an offset in eye position toward the injected site (opposite the visual position encoded at the site of injection), and the offset magnitude depended on the size of the target during fixation.

Offsets in the scatter of eye position were observed for the majority of our injected sites. In the sample experiment documented above, the average magnitude of the offset was bigger for the large target (radial amplitude, 1.2°) than for the medium (0.5°) or small (0.4°) targets. Figure 4 describes the mean radial amplitude of offsets for each target size and for each experiment in two monkeys. In most experiments, the offset magnitude increased with target size. However, in some experiments, it decreased with target size, whereas in others, it was larger or smaller for the medium target. Consequently, no significant correlation was found between the radial amplitude of offsets (y) and the diameter (x) of the targets ($R(x,y) = 0.21$; $p = 0.17$; $N = 41$). As we describe next, further analyses revealed that the change in eye position during fixation also depended on the site that was inactivated in the dSC.

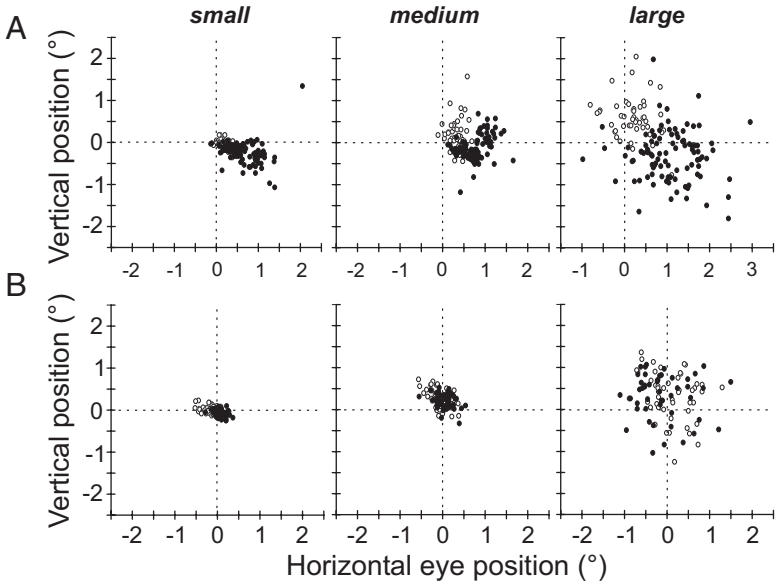

Figure 3. Effect of target size on the magnitude of the fixation offset after muscimol injection in the right rostral dSC (same sample experiment as in Fig. 2). ***A***, Average eye position measured over the entire fixation interval for each target size (left, small; middle, medium; right, large) and each trial recorded before (○) and after (●) injection of muscimol. After injection, eye position was offset to the lower right relative to baseline. ***B***, Effects of injecting saline solution in the same site in a separate, control experiment. No clear eye position offset was observed, suggesting that the offset in ***A*** was due to muscimol inactivation of dSC neurons.

Figure 5 plots the magnitude of the offset as a function of the eccentricity encoded at the injected dSC site for each target size (small, black symbols; medium, blue; large, red). After muscimol injection in the dSC (Fig. 5*A*), offsets were observed that depended on both the injected site and the target size. These effects were examined with two-way ANOVAs, made separately for each monkey, of the average horizontal and vertical eye position values as a function of the injection site and the target size. After muscimol injection, for each monkey, the horizontal and vertical eye positions during fixation depended on the site of injection (monkey A, $F_{(5,1098)} = 96.8$ and 75.9 for the horizontal and vertical eye positions, respectively; $p < 0.00001$; monkey W, $F_{(6,2955)} = 508.1$ and 230.1, $p < 0.00001$), the target size (monkey A, $F_{(2,1098)} = 63.8$ and 8.5, $p < 0.0005$; monkey W, $F_{(2,2955)} = 463.0$ and 1291.3, $p < 0.00001$), and also their interaction (monkey A, $F_{(10,1098)} = 66.6$ and 13.8, $p < 0.00001$; monkey W, $F_{(12,2955)} = 66.9$ and 89.1, $p < 0.00001$). After injection of saline solution (Fig. 5*B*), small but statistically significant offsets were also observed in both monkeys, possibly due to mechanical or chemical effects. However, they were contralesional (except for monkey A fixating the large target), and their magnitude did not increase with target size. The dependence of the offset on both target size and injection site after muscimol injection is consistent with the demonstration that eye position during fixation depends on a distributed population of dSC neurons, and that the size of this population is related to the size of the foveated target (Hafed and Krauzlis, 2008; Hafed et al., 2008). Thus, the pattern of eye position offsets observed during dSC inactivation can be explained by two factors—the target position signals suppressed by the inactivation and the range of target position signals normally recruited for each target.

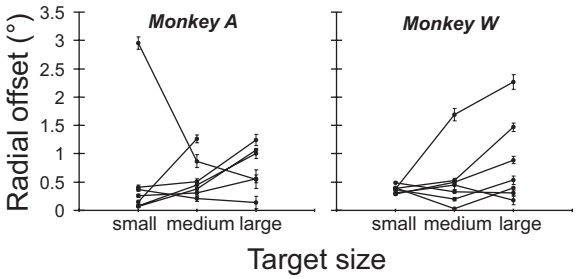

Figure 4. Summary of the effects of target size on the magnitude of the fixation offset measured for each experiment. The mean radial amplitude of offsets is plotted for each target size and for each experiment in two monkeys (error bars denote SEM). In both monkeys, an increase in the magnitude of the eye position offset was often observed with larger target sizes, but not always.

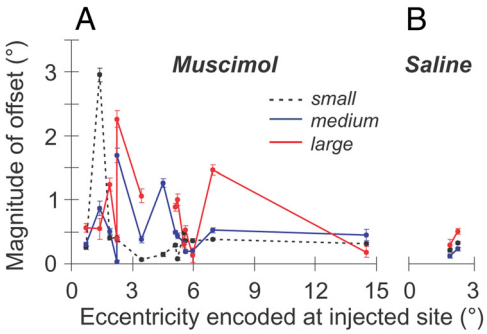

Figure 5. ***A***, ***B***, Summary of the effects of injecting muscimol (***A***) or saline solution (***B***) on the fixation of different target sizes. The plot in ***A*** shows the average magnitude of the inactivation-induced offset in eye position as a function of the eccentricity encoded at the injected dSC site for each target size (black, small target; blue, medium; red, large). The error bars denote SEM. The offset magnitude depended on the population of neurons that were inactivated, and the pattern of offsets was very similar to that seen in the same monkeys during smooth pursuit (Hafed et al., 2008).

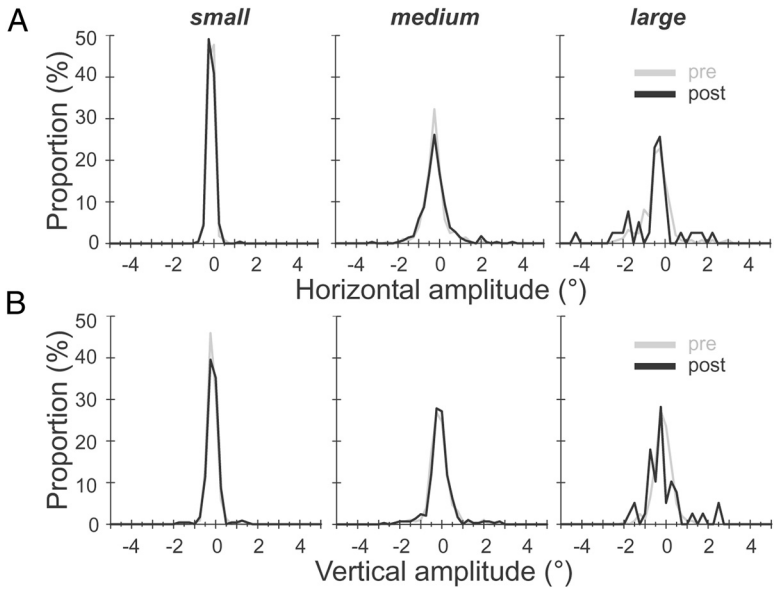

Figure 6. Effect of inactivating the rostral dSC on the distributions of fixational saccade amplitudes. ***A***, Distribution of horizontal amplitudes recorded before (gray) and after (black) injection of muscimol in the same site as in Figures 2 and 3. ***B***, Distribution of vertical amplitudes. There was no apparent asymmetry in the distribution of fixational saccade amplitudes as might be expected if the eye position offset was caused by dysmetric fixational saccades.

The eye position offset was not related to changes in fixational saccades

To test whether the postinjection offsets were due to dysmetric fixational saccades, we analyzed the distributions of fixational saccade amplitudes before and after muscimol injection into the SC. We found no asymmetries in these distributions. For example, the rightward offsets depicted in Figures 2 and 3 were not due to more frequent or larger rightward saccades than leftward ones. This can be seen clearly in Figure 6, which shows the distributions of horizontal (top) and vertical (bottom) amplitudes of fixational saccades before (gray) and after (black) injection of muscimol. Before muscimol injection, the horizontal amplitudes ranged from −0.5 to 0.6° [interquartile range (IQ), 0.2°; median of absolute amplitude values, 0.1°; $n = 222$] when the monkey fixated the small target. For the other targets, the horizontal amplitudes ranged from −2.4 to 2.3° (IQ, 0.4°; median, 0.2°; $n = 279$; medium target) and from −2.3 to 3.2° (IQ, 0.6°; median, 0.3°; $n = 246$; large target). The vertical amplitudes ranged from −0.8 to 1.1° (median ± IQ, 0.1 ± 0.3°) for the small target, from −1.9 to 2.2° (0.2 ± 0.5°) for the medium one, and from −1.8 to 1.5° (0.2 ± 0.5°) for the large one. Considering that the rostral dSC is involved in the generation of microsaccades (Hafed et al., 2009; Hafed and Krauzlis, 2012), this increase in the range of microsaccade amplitudes suggests that larger target sizes increase the extent of the population of active neurons in the rostral dSC during fixation. After muscimol injection, the distributions of amplitude values did not change. The horizontal amplitude of fixational saccades (small target, 0.1 ± 0.2, $n = 230$; medium, 0.5 ± 0.6, $n = 287$; large, 0.8 ± 0.5°, $n = 39$) was not significantly different from that observed before the injection (Mann–Whitney test, p values >0.50). Likewise, the vertical amplitude of fixational saccades (small, 0.2 ± 0.3°; medium, 0.4 ± 0.4°; large, 0.6 ± 0.9°) was not altered either (p values >0.50). Similar observations were made for the other injection sites.

Muscimol injection also reduced the proportion of microsaccades generated while the monkey was fixating the central target, indicating that the offset was not due to a problem in maintaining fixation or suppressing unwanted saccades. Figure 7*A* shows for each target size the microsaccade rate before (abscissa) and after muscimol injection (ordinate). The rate of microsaccade production was significantly reduced in 8 of 14 experiments when the small target was presented (19% average reduction), in 7 of 14 experiments with the medium target (18% average reduction), and 6 of 13 experiments with the large one (15% average reduction). Thus, consistent with the target location hypothesis (Hafed et al., 2008, 2009) and inconsistent with the dichotomist hypothesis proposed by Munoz and Wurtz (1993b), inactivation of the rostral dSC altered eye position and reduced the rate of fixational saccades without disrupting the ability to maintain fixation. Figure 7*B* shows the change in microsaccade frequency as a function of the eccentricity encoded at the injected site. The microsaccade rate was most affected by the more rostral injection sites, but that effect was also seen at sites extending out to ~4°, consistent with the distribution of observed modulated dSC neurons during microsaccades (Hafed and Krauzlis 2012).

Although previous studies have shown that muscimol injection in the dSC altered the velocity of saccades toward peripheral targets (Hikosaka and Wurtz, 1985; Sparks et al., 1990; Quaia et al., 1998), our data do not indicate any change in the velocity of fixational saccades after muscimol injection in the rostral SC. Figure 8 shows the relationship between the radial amplitude and peak velocity of saccades recorded during the same sample experiment as described in Figures 2, 3, and 6. Like the preinjection saccades, those recorded after the injection of muscimol had a peak velocity that increased with their amplitude. However, no evidence was found that would suggest a slowing of fixational saccades of any particular amplitude. Similar observations were made in all experiments. These results indicate that the offsets were not caused by a deficit or abnormality in the execution of fixational saccades.

Saccades to peripheral targets largely compensated for the eye position offsets during fixation

After muscimol injection in the rostral half of the dSC, only small changes in accuracy were observed in the large saccades directed toward the peripheral targets. Figure 9 describes the dysmetria observed for each of the four targets. Small undershoots were observed in contralateral saccades (Fig. 9*A*), and the paired comparison between the preinjection and postinjection median values confirmed a statistically significant trend (Wilcoxon test, $p < 0.01$). Concerning the ipsilateral (Fig. 9*B*), downward (*C*), and upward (*D*) saccades, no consistent change affected their accuracy (p values >0.05). To test whether the small hypometria (−0.5 ± 0.4°) of contralateral saccades was related to the ipsilesional fixation offset, we tested the correlation between the magnitude of the hypometria (y) and the size of the fixation offset (x) across all experiments. No significant correlation was found whether the target was small, medium, or large (Bravais–Pearson correlation coefficients, $R(x,y) = 0.20$, 0.04, and 0.20, respectively). Thus, saccades to the peripheral targets compensated for

the initial eye position error caused by the fixation offset. Visual feedback provides a simple explanation for this compensation: even though the peripheral target appeared at a slightly different retinal eccentricity after dSC inactivation (because of the offset in fixation eye position), they recruited a population of neurons in the caudal dSC that was relatively unaffected by the injection.

Furthermore, for the experiment that led to the largest horizontal offset (Fig. 4, monkey A), no significant correlation was found between the initial and final horizontal eye positions (Fig. 10*B*, *B4*). In summary, we could not find any evidence suggesting that the hypometria of contralateral saccades was due to changes in starting eye position. Significant correlations were occasionally observed between the initial and final horizontal eye positions for a specific target (Fig. 10*B*, *B3*). However, such correlations were absent in the majority of the experiments, whether the target size was small (no correlation in 65–86% cases), medium (no correlation in 85% of cases), or large (no correlation in 60–84% of cases).

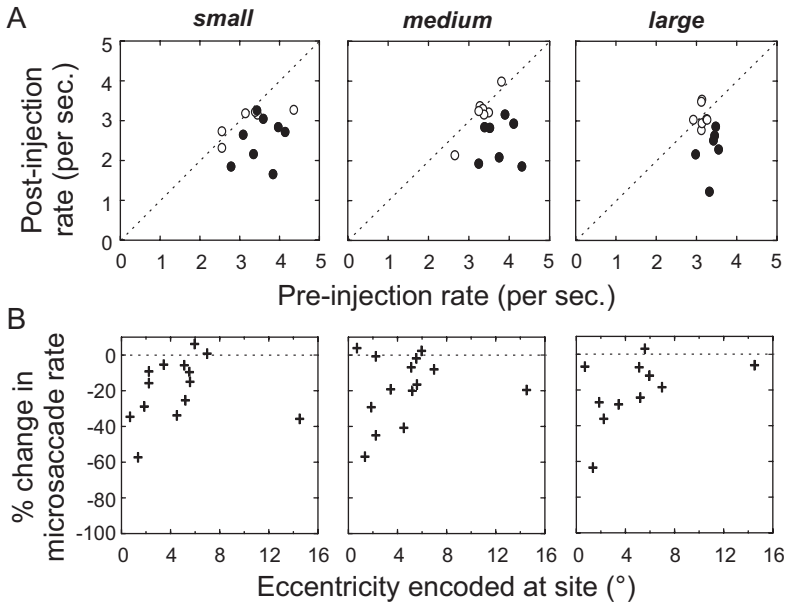

Figure 7. Summary of the effects of dSC inactivation on the rate of microsaccades generated during fixation of each target size (left, small target; middle, medium; right, large). ***A***, Postinjection rate against preinjection rate. If anything, inactivation caused a reduction of saccade frequency rather than an increase, as might have been expected from the view of the rostral dSC as a region suppressing saccade generation. Filled symbols denote statistically significant differences between preinjection and postinjection rates ($p < 0.05$). ***B***, Percent change in microsaccade frequency against eccentricity encoded at the injected site.

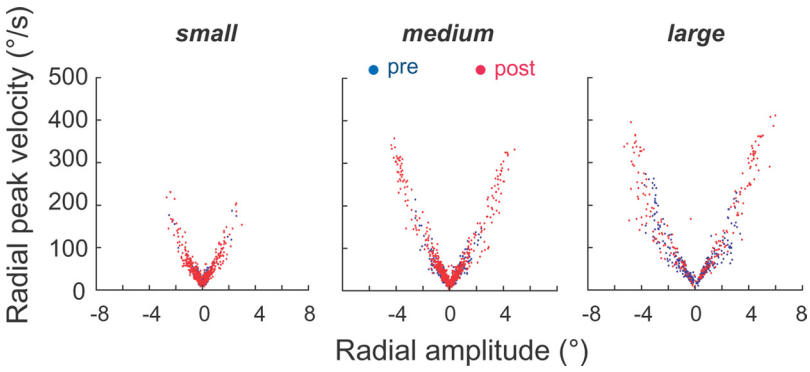

Figure 8. Effect of inactivating the rostral dSC on the velocity of fixational saccades. The relationship between the radial amplitude and peak velocity is shown for all saccades generated while the monkey fixated on the central target (left, small target; middle, medium; right, large) before (blue) and after (red) muscimol injection. The same sample experiment as in Figures 2, 3, and 6 was used. No apparent change was caused by muscimol inactivation.

Because muscimol injection in the rostral dSC was shown previously to alter the latency and velocity of saccades toward the peripheral targets (Munoz and Wurtz, 1993b), we also examined these aspects of the saccade performance. Overall, we found variable effects that depended on the target location. Figure 11 shows the median values of saccade latency before and after muscimol injection for each cardinal direction. When the peripheral target was located in the visual field contralateral to the injected side (Fig. 11*A*), the latency of saccades was significantly increased in 12 of 14 experiments (Mann–Whitney test, $p < 0.05$); on average, it was 40 ms longer (26% increase; nonparametric Wilcoxon test for paired comparison, $p < 0.01$). When the peripheral target was located in the visual field ipsilateral to the injected side (Fig. 11*B*), the latency was significantly reduced in 12 experiments and increased in one experiment. On average, the latency of ipsilateral saccades was 19 ms shorter after muscimol injection (13% decrease; $p < 0.01$). For the lower visual field (Fig. 11*C*), the latency was reduced in 11 experiments and increased in 2 experiments (18 ms or 10% average decrease; $p < 0.01$). Finally, the latency of upward saccades was not affected in a consistent manner (Fig. 11*D*). It was significantly reduced in three experiments and increased in four experiments (3 ms average increase corresponding to a 1% change).

Concerning the peak velocity of saccades toward the peripheral targets, changes that depended on the location of the target relative to the injected site were also observed. For contralesional saccades, the horizontal peak velocity was significantly reduced in 9 experiments and increased in 2 of 14 experiments; on average, the median horizontal peak velocity was reduced by 12% after muscimol injection ($p < 0.05$). For ipsilesional saccades, significant increases in horizontal peak velocity were found in nine experiments (decreases in two experiments); on average, the median horizontal peak velocity was increased by 9% after muscimol injection ($p < 0.01$). For upward and downward saccades, significant changes in vertical peak velocity were occasionally observed. The paired comparison of preinjection versus postinjection median values failed to reveal any trend for an increase or decrease in the vertical peak velocity of these saccades after muscimol injection. Interestingly, a significant correlation was found between the latency changes (x) and the peak velocity changes (y) for contralesional saccades (Fig. 12*A*; $R(x,y) = -0.74$, $p < 0.01$), but not for ipsilesional (Fig. 12*B*) or vertical saccades (*C*,*D*). Thus, the sites that led to larger increases in the latency of contralesional saccades also produced larger reductions in peak velocity. These correlated changes suggest that the involvement of the dSC in the triggering and dynamics of saccades rest on shared

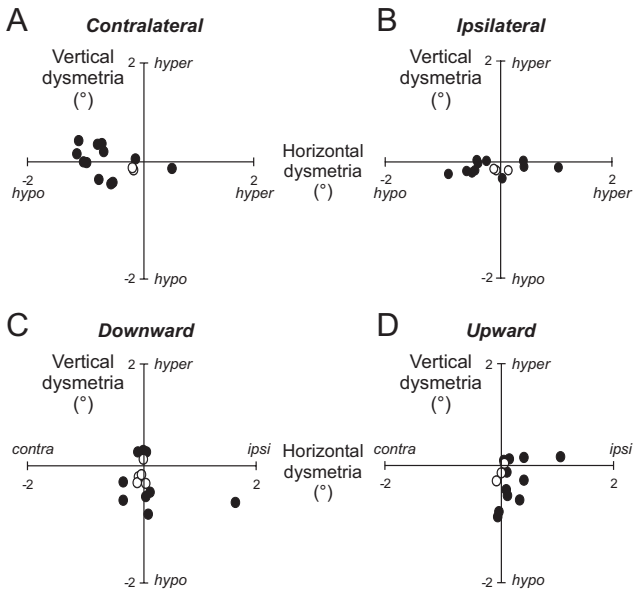

Figure 9. Summary of the effects of dSC inactivation on the accuracy of saccades toward the peripheral targets. ***A–D***, Each plot describes for each peripheral target location (target in the contralateral visual field, ***A***; target in the ipsilateral field, ***B***; target in the lower visual field, ***C***; and target in the upper visual field, ***D***) the horizontal and vertical dysmetria of saccades. Filled symbols indicate the differences between the preinjection and postinjection amplitude values that were statistically significant (Mann–Whitney test, $p < 0.05$).

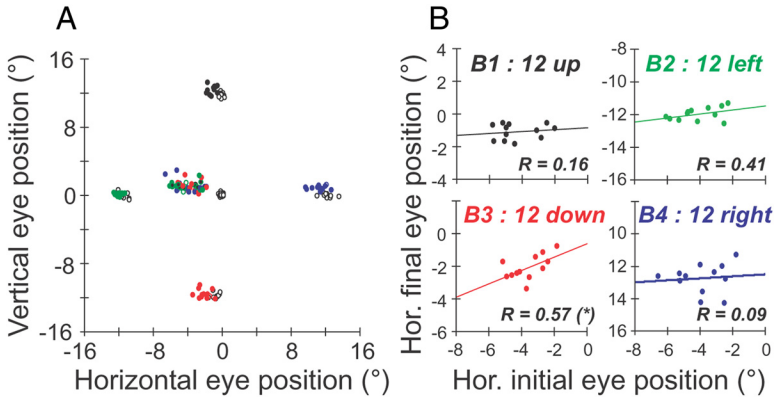

Figure 10. Accuracy of saccades to the peripheral targets for the experiment that led to the largest horizontal offset (Fig. 4, monkey A). ***A***, Scatter of initial and final eye positions before (open symbols) and after (filled symbols) muscimol injection. Different colors are used to label the saccades toward the different targets (black, 12° up; blue, right; red, down; green, left). ***B***, Relationship between the initial and final horizontal eye positions for each target. *R* values correspond to the Bravais–Pearson correlation coefficients. Despite a large offset during fixation, the targeting saccades to the periphery were relatively accurate.

processes (see also Sparks et al., 1990, Figs. 3*C*, 5*A*; for comparable observations using electrical microstimulation techniques, see Stanford et al., 1996). The changes that affect contralesional saccades likely result from a diffusion of muscimol toward the site encoding the tested peripheral target (see Materials and Methods), whereas those altering ipsilesional saccades could result from disinhibition of neurons in the opposite dSC via inhibitory intercollicular connections (May, 2006; Takahashi et al., 2010).

Discussion

Our study provides evidence that bilateral activity within the rostral half of the dSC encodes the location of a foveal target, analogous to the way that population activity in caudal parts of the dSC encodes the locations of peripheral targets (Lee et al., 1988). After unilateral local injection of muscimol, a shift was observed in the scatter of eye positions when the animal fixated a visual target (Figs. 2–5). This offset cannot be explained if one considers that fixation is accomplished by the rostral dSC solely through an inhibitory process that suppresses the generation of saccades (Munoz and Wurtz, 1993b). Instead, if one considers fixation as an equilibrium defined by the population average of fluctuating target position signals from the two dSCs, then the fixation offset merely establishes the foveal visual stimulation that is required to restore the balance of activity between the two dSCs. By silencing a subset of dSC signals, injection of muscimol in one dSC shifts the center of gravity of bilateral activity toward the opposite dSC, i.e., toward locations in the visual field ipsilateral to the injected side.

The dependence of the offset magnitude on both the target size and injected site (Figs. 3–5) (Hafed et al., 2008) indicates that the offset results from an interaction between the extent of foveal stimulation induced by the fixated target and the position vectors encoded at the injected site. This dependence likely reflects the extent to which the inactivation affects the population of neurons that are recruited: the fixation offset reflects the new equilibrium reached after silencing a portion of these neurons. The larger range of fixational saccade amplitudes with larger target sizes (Figs. 6, 8) (Sandrine et al., 2006) also suggests that larger target sizes expand the population of active neurons during fixation (Hafed and Krauzlis, 2012). The fixation offsets cannot be explained by changes in saccade generation because there were neither asymmetrical distributions in the amplitude of fixational saccades (Fig. 6) nor changes in their velocity (Fig. 8).

Comparison with previous studies

Mismatches between the eye and target positions during fixation have been observed previously following large lesions (Albano and Wurtz, 1982; Keating et al., 1986) and cooling (Keating and Gooley, 1988) in the dSC. In these studies, an eye position dependency was observed in the magnitude of offsets that may result from the influence of ascending projections from the nucleus prepositus hypoglossi (Hartwich-Young et al., 1990). After muscimol injection in the rostral dSC, Basso et al. (2000) also noticed an ipsilateral fixation offset. Interestingly, when bicuculline ($GABA_A$ antagonist) is injected, the offset seems to be contralateral (Munoz and Wurtz, 1993b, their Fig. 8). If bicuculline disinhibited neurons in the rostral dSC and increased their spontaneous activity, then the contralateral offset indicates that the gaze direction during fixation is determined by the balance of activity across the two dSCs. Gaze deviates toward the side that is less active: toward the opposite side after bicuculline injection and toward the injected side after muscimol injection.

Fixation offsets were also observed when GABAergic agents were injected in a cerebellar nucleus that projects toward the rostral dSC, the caudal fastigial nucleus (cFN) (May et al., 1990). Indeed, muscimol injection in this region led to an ipsilateral fixation offset (Robinson et al., 1993; Goffart et al., 2004; Guerrasio et al., 2010), whereas the offset was contralateral after bicuculline injection (Sato and Noda, 1992). However, unlike dSC inactivation, inactivation of cFN affected the amplitude of mic-

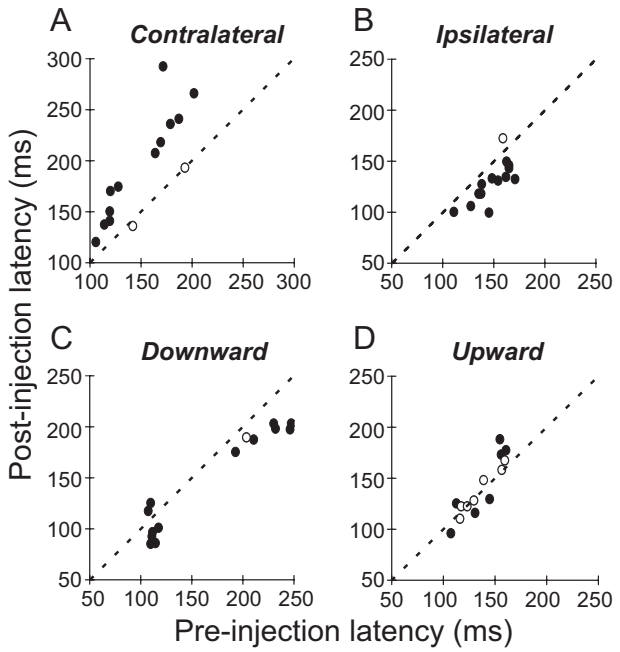

Figure 11. Summary of the effects of dSC inactivation on the latency of saccades toward the peripheral targets. ***A–D***, Median values of latencies before and after injection for each cardinal direction. Filled symbols indicate the differences between the preinjection and postinjection latency values that were statistically significant (Mann–Whitney test, $p < 0.05$). Depending on the direction of the saccade, there were either increases or decreases in saccade latency.

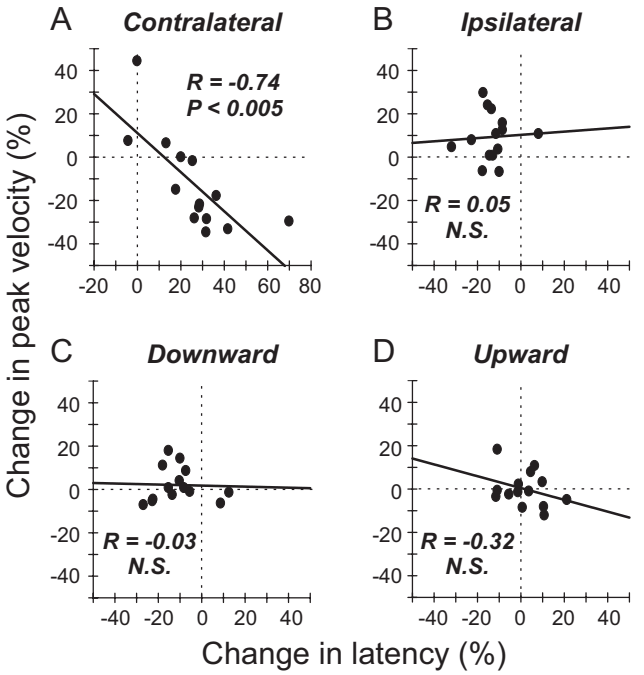

Figure 12. Effects of dSC inactivation on the peak velocity of saccades toward the peripheral targets (12° eccentricity) and their relationship to the changes in latency. ***A–D***, Percent changes in latency (abscissa) and in horizontal (***A***, ***B***) and vertical (***C***, ***D***) peak velocity (ordinate) are shown for each cardinal direction. For contralesional saccades (***A***), the sites whose inactivation led to the larger increases in saccade latency were associated with larger reductions in peak velocity.

rosaccades. According to Guerrasio et al. (2010), the fixation offset results from a perturbation of the fastigiocollicular influence, whereas the changes in the horizontal amplitude of microsaccades from a dysfunction of the fastigioreticular influence. The different effects of dSC versus cFN inactivation are consistent with the hypotheses that the population of active neurons in the dSC encodes the location of targets using a place (topographical) code (Robinson, 1972; Schiller and Stryker, 1972; Wurtz and Goldberg, 1972), while bilateral cFN activity is involved in regulating the balance of activity between the left and right saccade generators, i.e., setting the equilibrium point of bilateral dSC activity with their sustained firing rate during fixation (Guerrasio et al., 2010) and regulating the balance between the excitatory and inhibitory drives that impinge upon the agonist motoneurons with their saccade-related bursts (Goffart et al., 2004; Fuchs et al., 2010).

Fixation offsets have also been observed after muscimol injection in the frontal eye field (Dias and Segraves, 1999), a cortical region that projects to the dSC (Segraves and Goldberg, 1987; Stanton et al., 1988) as well as to the nucleus raphe interpositus (RIP) in the caudal pontine reticular formation (Segraves, 1992), possibly for the maintenance of fixation (Izawa et al., 2009). The RIP, which is the target of projections from the rostral dSC (Strassman et al., 1987; Gandhi and Keller, 1997; Büttner-Ennever et al., 1999; Sugiuchi et al., 2005), comprises omnipause neurons that display a sustained discharge during intersaccadic intervals and pause during saccades (Everling et al., 1998; Phillips et al., 1999) and microsaccades (Van Horn and Cullen, 2012). This nucleus is considered a pivotal structure between orienting and maintaining steady gaze, primarily because its microstimulation delays the generation of saccades (Paré and Guitton, 1998; Gandhi and Sparks, 2007). However, its neurotoxic lesion (Kaneko, 1996) or inactivation by muscimol (Soetedjo et al., 2000) does not shorten the latency of saccades, but increases their duration.

A new framework for the neural control of foveation during fixation

Until recently, the dSC was considered to be composed of two zones that inhibit each other in a push–pull manner: a fixation zone located in the rostral dSC and a saccade zone located more caudally (Munoz and Guitton, 1991; Munoz and Wurtz, 1993a,b). According to this dichotomist model, the fixation zone inhibits the generation of saccades through its inhibitory projections toward the saccade zone, but also through excitatory projections toward the RIP. Fixation was essentially considered as an inhibitory process that maintains gaze directed toward a target by preventing saccades to other targets. This view was based on three major observations. First, the activity of rostral dSC neurons is sustained when a visual target is being fixated and declines after its extinction (Dorris and Munoz, 1995). Second, electrical microstimulation in the rostral dSC delays the triggering of saccades toward peripheral targets (Munoz and Wurtz, 1993b; Paré and Guitton, 1994). Finally, local injection of muscimol leads to irrepressible saccades toward a peripheral target even though the monkey is required to maintain fixation on a central target (Munoz and Wurtz, 1993b).

Our alternative view proposes that fixation is an equilibrium established by the population average of fluctuating target position signals issued bilaterally from the dSCs. As shown in our results as well as in some pathological (Sato and Noda, 1992; Dias and Segraves, 1999; Guerrasio et al., 2010) or even normal (Goffart et al., 2006) cases, stable fixation can be engaged even though the gaze is not accurately directed toward the target location. We propose that such fixation offsets reestablish the balance of activ-

ity that the foveal stimulation evokes within the two dSCs (Hafed et al., 2008). This model can also explain the major observations upon which the dichotomist model was based. First, the changes in neuronal activity in the rostral dSC would be related to the presence or absence of a foveal goal. Second, the delayed triggering of visual saccades during electrical microstimulation of the rostral dSC would be caused either by an enhancement of signals encoding the foveal goal to the detriment of those encoding peripheral targets, or by the nonspecific recruitment of inhibitory afferents. Finally, the irrepressible saccades observed after muscimol injection in the rostral dSC would result from weakened signals encoding the foveal target location, i.e., reducing its competitiveness when a peripheral target is simultaneously presented.

Unlike the dichotomist model, the equilibrium model can also explain the contribution of the rostral dSC in the generation of microsaccades: the microsaccades that occur during sustained fixation would result from transient imbalances of activity between the two rostral dSCs (Hafed et al., 2009; Hafed and Krauzlis, 2012). The reduced microsaccade rate after muscimol injection (Fig. 6) suggests that the occurrence of such transient imbalances depends on the number of active neurons in the rostral dSC. Moreover, microsaccade rate was affected for a range of sites in the rostral half of the SC, and not just at the far rostral pole. This is consistent with the distribution of active neurons in the dSC during microsaccades, which is not restricted to the rostral pole, but extends out to ~4° in the dSC map (Hafed et al., 2009; Hafed and Krauzlis, 2012). Thus, an attractive feature of the equilibrium model is that it can explain the control of fixation and the triggering of saccades, regardless of the target eccentricity or the saccade amplitude.

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